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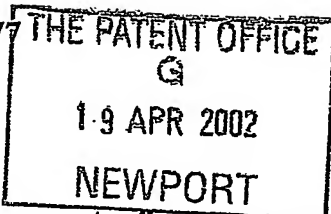
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2. Patent Application Number (the Patent Office will fill in this part)	0208945.6		19APR02 E712334-4 002884 P01/7700 0.00-0208945.6
3. Full name, address and postcode of the or of each applicant (underline all surnames)	The Queen's University of Belfast University Road Belfast BT7 1NN Northern Ireland		
Patents ADP number (if you know it)			
If the applicant is a corporate body, give the country/state of its incorporation	889675001		
4. Title of the invention	"Vascular Impedance Measurement Apparatus"		
5. Name of your agent (if you have one)	Murgitroyd & Company		
"Address for service" in the United Kingdom to which all correspondence should be sent (including the postcode)	Scotland House 165-169 Scotland Street GLASGOW G5 8PL		
Patents ADP number (if you know it)	1198013		
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a) any applicant named in part 3 is not an inventor, or			
b) there is an inventor who is not named as an applicant, or	Yes		
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I/We request the grant of a patent on the basis of this application

Signature *Murgitroyd & Co.*  
Murgitroyd & Company

Date  
18 April 2002

2. Name and daytime telephone number of  
person to contact in the United Kingdom

Mark Earnshaw 0141 307 8400

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1     Vascular Impedance Measurement Apparatus

2

3

4     **Introduction**

5     The present invention relates to apparatus for  
6     measuring vascular impedance.

7

8     The complications of cardiovascular disease  
9     represent the leading cause of morbid and mortal  
10    events in Western society. At present, diagnostic  
11    procedures are designed to assess the extent and  
12    severity of blood vessel damage when symptoms  
13    present or with the occurrence of vascular events.  
14    The diagnostic challenge is to detect abnormal  
15    structure and function in the vascular system at an  
16    early pre-clinical stage. The ability to detect and  
17    monitor sub-clinical arterial damage has the  
18    potential to refine cardiovascular risk  
19    stratification and enable early intervention to  
20    prevent or attenuate disease progression.

21

1 Traditionally, the arterial circulation has been  
2 considered a steady-flow system characterised by  
3 mean arterial pressure that represents the product  
4 of cardiac output and total peripheral resistance.

5  
6 The pulsatile component of pressure is determined by  
7 the pattern of left ventricular ejection and the  
8 stroke volume. The compliance characteristics of the  
9 arterial circulation has been largely ignored in  
10 prior haemodynamic studies.

11  
12 The importance of assessing arterial wall integrity  
13 has been highlighted by studies demonstrating that a  
14 reduction in the pulsatile function or compliance  
15 characteristics of large arteries represents a  
16 powerful independent risk factor for future  
17 cardiovascular events. Accumulating evidence  
18 suggests that abnormalities in the pulsatile  
19 characteristics of arteries occur early in disease  
20 processes associated with increased cardiovascular  
21 risk. Importantly, impaired pulsatile arterial  
22 function is recognised as an independent predictor  
23 of risk for vascular events in patients with various  
24 disease states including coronary heart disease,  
25 congestive heart failure, hypertension and diabetes  
26 mellitus.

27  
28 Studies relating outcome to abnormalities in  
29 pulsatile function have focused on large arteries,  
30 although analysis of arterial pressure pulse  
31 waveforms suggest that the earliest abnormalities in

1     arterial structure and function resides in the  
2     microcirculation.

3

4     The study of this section of the vasculature has  
5     been hindered by the lack of a non-invasive,  
6     reproducible and repeatable technique capable of  
7     assessing the compliance characteristics or  
8     pulsatile function of small arteries and arterioles.

9

10    Physiologically, the impedance load or opposition to  
11    flow presented by the circulation is measured  
12    invasively by analysing the altered pressure/flow  
13    relationships and pulse contour parameters produced  
14    through the effects of disease on the structural and  
15    functional components of the arterial system. Input  
16    impedance relates simultaneously recorded pressure  
17    and flow waveforms under specific mathematical  
18    conditions. The haemodynamic properties of the  
19    system can be quantified as the impedance concept  
20    permits the heart and arteries to be considered  
21    separately and their interaction understood as a  
22    function of pump and load properties. As pressure  
23    and flow waves are periodic and continuous, Fourier  
24    series methods can be used to generate the impedance  
25    function. The modulus at each harmonic in the  
26    Fourier series is the ratio of the pressure modulus  
27    to the flow modulus at that harmonic and the phase  
28    at each harmonic is the difference between pressure  
29    phase and flow phase at the same harmonic. As the  
30    impedance of a vascular bed varies with frequency,  
31    complete specification of pulsatile pressure and

1 flow relationships takes the form of the spectrum of  
2 moduli and phase angles versus frequency<sup>5</sup>.

3  
4 Characteristic impedance (the inverse of arterial  
5 compliance) defines the relationship between  
6 pressure and flow in an artery or arterial network  
7 when pressure and flow waves are not influenced by  
8 wave reflections. These conditions do not exist in  
9 the arterial system and the input impedance values  
10 oscillate around the characteristic impedance value  
11 because of wave reflection. Wave reflections are  
12 known to exert their greatest influence on impedance  
13 moduli at low frequencies. For higher frequencies,  
14 the input impedance approaches the characteristic  
15 impedance which has been estimated in prior  
16 haemodynamic studies as the arithmetic mean of input  
17 impedance moduli above 2-4 Hz.

18  
19 In the prior art, detailed studies of arterial  
20 pressure and flow are only possible through the use  
21 of invasive techniques. Such techniques cannot be  
22 used to monitor changes in the circulatory system of  
23 a patient over time because of the dangers to health  
24 posed by these techniques.

#### 25 26 **Statements of Invention**

27  
28 In accordance with a first aspect of the present  
29 invention there is provided apparatus for the  
30 measurement of vascular impedance of the ocular  
31 micro circulation *in vivo*; the apparatus comprising  
32 intra-ocular pressure measurement means, from which

1 a pressure pulse waveform is calculable and blood  
2 velocity profile measurement means for measuring the  
3 linear blood flow velocity in the retrobulbar  
4 circulation, means for calculating the vascular  
5 impedance modulus from the pressure pulse waveform  
6 and the linear blood flow velocity .

7  
8 Preferably the arterial pulse waveform measurement  
9 means measures the maximum and minimum pressure  
10 values of the pulse profile to calculate a mean  
11 intra-ocular pressure.

12  
13 Preferably, an ocular pneumotonometer is used to  
14 measure intra-ocular pressure.

15  
16 Preferably the blood velocity profile measurement  
17 means is an ultrasound device.

18  
19 Preferably the ultrasound device is a doppler  
20 ultrasound imager.

21  
22 Preferably the change in the pulsatile intra-ocular  
23 pressure waveform and the linear blood flow velocity  
24 are measured sequentially.

25  
26 Preferably, the means for calculating the vascular  
27 impedance modulus comprises obtaining the fourier  
28 transform of the intra-ocular pressure pulse  
29 waveform and the linear blood flow velocity and  
30 dividing the transformed values of the pulsatile  
31 change in the intra-ocular pressure pulse by the  
32 transformed retrobulbar blood flow velocity.



1  
2 Preferably the pulsatile change in intra-ocular  
3 pressure has a phase associated therewith.  
4

5 Preferably the intra-ocular blood velocity has a  
6 phase associated therewith.  
7

8 In accordance with a second aspect of the present  
9 invention there is provided a method for the  
10 measurement of vascular impedance of the ocular  
11 micro circulation *in vivo*, the method comprising the  
12 steps of: measuring the intra-ocular pressure pulse  
13 waveform of the ocular network;  
14 measuring the linear blood flow velocity in the  
15 retrobulbar circulation; and  
16 calculating the vascular impedance modulus from the  
17 intra ocular pressure pulse waveform and the linear  
18 blood flow velocity waveform.  
19

20 Preferably, the change in the pulsatile intra-ocular  
21 pressure waveform and the linear blood flow velocity  
22 are measured sequentially.  
23

#### 24 **Specific Description**

25

26 The invention will now be described by way of  
27 example only with reference to the accompanying  
28 drawings in which:  
29

30 Fig.1 is a diagram of an eye having means for  
31 measuring the intra-ocular pressure using the

1 principle of applanation tonometry at the front of  
2 the eye;

3

4 Fig.2 is a diagram of an eye having means for  
5 measuring the linear flow velocity by interrogating  
6 the retrobulbar circulation from the front of the  
7 eye;

8

9 Fig.3 is a graph of the periodic pressure signal as  
10 measured using the present invention plotted against  
11 time;

12

13 Fig.4 is a graph of the periodic velocity signal as  
14 measured using the present invention plotted against  
15 time;

16

17 Fig.5 is a graph of impedance modulus plotted  
18 against frequency; and

19

20 Fig.6 is a graph of phase plotted against frequency.

21

22 Figs. 1 and 2 show a first embodiment of the present  
23 invention. Figs.1 and 2 are diagrams showing some  
24 features of the human eye 1. These include the  
25 optic nerve 3, the ophthalmic artery 5, a bolus of  
26 blood contained in the ophthalmic artery 5  
27 positioned outside the ocular vascular network 9.  
28 The vein 11 is also shown.

29

30 Fig.1 also shows the means for measuring the intra-  
31 ocular pressure 13; provided, in this example by a  
32 tonometer system applanated to the cornea 23.

1  
2 Fig.2 shows means for measuring the linear blood  
3 flow velocity in the retrobulbar circulation 17,  
4 connected to the front of the eye. This is an  
5 ultrasonic device that is placed on the eyelid  
6 19, the eyelid 19 being covered with a gel 21 to  
7 ensure that the ultrasound device is properly  
8 coupled to the eye 1. This device measures the  
9 linear velocity of the bolus of blood 7 in the  
10 ophthalmic artery 5.

11  
12 In use, the tonometer system 13 employs continuous  
13 airflow pneumotonometry with a probe 15 applanated  
14 on the cornea to record intraocular pressure using a  
15 pneumatic sensor. The device samples at 200 Hz with  
16 a resolution of 0.01 mmHg and the signals are  
17 acquired over a 20 second period. Pulsatile  
18 variation of intraocular pressure results from  
19 pressure oscillations generated by cardiac  
20 contraction altering the distending pressure in the  
21 vessel walls. Compliance of an artery, or an entire  
22 arterial bed, describes the ability to store a  
23 varying amount of blood. Changes in volume within  
24 the ocular vascular bed will produce an equal change  
25 in volume. The pulsatile ocular waveforms are  
26 recorded after administration of oxybuprocaine 0.4%  
27 drops to anaesthetise the cornea.

28  
29 The variation in intra-ocular pressure as a function  
30 of time reflects the introduction of the bolus of  
31 blood 7 into the ocular vascular network 9. The

1    ocular vascular network 9 expands to accommodate the  
2    additional volume of blood.

3

4    As the intra-ocular fluids are incompressible, the  
5    intra-ocular pressure response to the volume change  
6    will depend of the viscoelastic properties of the  
7    vessel network and the ocular rigidity. The  
8    mechanical properties and distending pressures will  
9    vary at different sites in the ocular vascular  
10   network 9 and it is the composite effect of these  
11   influences that determine the intra-ocular pressure  
12   waveform morphology. Whilst the rigidity of the  
13   ocular coat can vary between individuals, the half-  
14   life of the collagen and elastin components are  
15   measured in years. Consequently, the characteristics  
16   of these boundary structures would not be expected  
17   to change significantly within an individual over a  
18   period of weeks or months. Therefore changes  
19   recorded in the intra-ocular pressure pulse waveform  
20   will be reflective of alteration in the viscoelastic  
21   properties of the ocular microcirculatory bed.

22

23   The present invention uses the directly recorded  
24   change in intra-ocular pressure in its analysis and  
25   not the generated flow output measurements from the  
26   device that relate pressure change to volume change  
27   within the eye. The pulsatility of the intra-ocular  
28   pressure is dependent on the pulsatile inflow and  
29   distension of the vessels which is related to the  
30   viscoelastic properties of the ocular circulation.  
31   Scleral rigidity may limit the frequency of pressure

1 fluctuations but does not cause variation in  
2 pressure.

3

4 In the example shown in Fig.2, a colour doppler  
5 ultrasound imager 17 is used to examine the blood  
6 velocity waveform in the retrobulbar ocular  
7 circulation. This technique employs simultaneous B-  
8 scan and doppler imaging to allow location and  
9 identification of blood vessels. The sample volume  
10 defined by the imager 17 is placed over a vessel of  
11 interest, in this case, the bolus of blood 7 and the  
12 frequency shifts received are assembled into a  
13 spectral waveform. The spectral waveform represents  
14 the cumulative frequency shifts present and can be  
15 displayed as a time-velocity waveform.

16

17 In use, alternate measurements of the arterial pulse  
18 waveform and blood velocity profile are taken.  
19 The shape of the linear velocity flow waveform,  
20 recorded in the retrobulbar circulation, is  
21 determined by and is critically dependent on changes  
22 in total cross-sectional area of the ocular vascular  
23 network.

24

25 Like pressure, flow will also vary at different  
26 sites in the ocular vascular network 9 and the  
27 velocity waveform morphology therefore reflects the  
28 status of the entire ocular vascular network 9. In  
29 essence, the flow velocity waveform derived from the  
30 retrobulbar circulation and the intra-ocular  
31 pressure waveform reflect the sum total of the

1 various calibre and pressure changes throughout the  
2 ocular vascular bed.  
3 Measured over time, changes in the linear flow  
4 waveform can provide information on changes in the  
5 ability of the ocular vascular network to expand  
6 during the cardiac cycle. Such information can lead  
7 to early diagnosis and subsequent early treatment of  
8 disease.

9  
10 The present invention uses linear velocity of flow  
11 in calculating the vascular impedance of the  
12 microcirculation as changes in velocity of flow are  
13 determined by changes in the total cross-sectional  
14 area of the ocular vascular network 9. Furthermore,  
15 the use of linear velocity of flow permits  
16 comparisons of impedance moduli derived from  
17 different arteries and in the same artery under  
18 varying conditions. This comparison cannot be  
19 validly made using volume flow measurements.

20  
21 Typical examples of intraocular pressure and  
22 velocity profiles (obtained from the ophthalmic  
23 artery) are shown in Figures 3 and 4.

24  
25 Fig. 3 is a graph of pressure plotted with respect  
26 to time. The figure shows the periodicity of the  
27 pressure fluctuation. The cardiac cycle can be  
28 identified from the period of the pressure  
29 fluctuation as being approximately 0.9 s.

30

31 Fig. 4 is a graph of linear blood velocity plotted  
32 with respect to time. The figure shows the

1 periodicity of linear velocity fluctuation. The  
 2 cardiac cycle can be identified from the period of  
 3 the linear velocity fluctuation as being  
 4 approximately 0.9s.

5  
 6 The sites of data acquisition enable the recording  
 7 of pressure and linear velocity waveforms that  
 8 provide information about the entire ocular vascular  
 9 network and not merely single vessel in the network.  
 10 Measurements are obtained sequentially using the  
 11 tangent method to align pressure and velocity  
 12 waveforms. This technique is employed to ensure  
 13 effective alignment of waveforms for analysis. The  
 14 signals may also be gated to an ECG. Other known  
 15 methods may also be employed.

16  
 17 As seen in Figures 3 and 4, the velocity and  
 18 pressure signals are periodic and time dependent and  
 19 can thus be represented in the frequency domain by  
 20 obtaining their Fourier transform:  $P(\omega) = FT [P(t)]$   
 21 and  $V(\omega) = FT[V(t)]$  where FT represents Fourier  
 22 transformation. In addition, each frequency  
 23 component of pressure and velocity will have its own  
 24 associated phase ( $\phi_p$  pressure phase,  $\phi_v$  velocity  
 25 phase). The frequency dependent impedance modulus  
 26 and phase can be determined from:  $Z(\omega) = P(\omega)/V(\omega)$   
 27 and  $\phi(\omega) = \phi_p(\omega) - \phi_v(\omega)$ .

28  
 29 Figures 5 and 6 show typical plots of  $Z(\omega)$  and  $\phi(\omega)$   
 30 for a normal subject.

31

1 The flow and first derivative of pressure occur at  
2 similar time points. As pressure and flow are  
3 obtained sequentially the first derivative of the  
4 pressure waveform is aligned to the flow waveform.  
5 A tangent to end diastole and a tangent to the  
6 initial upstroke in pressure wall intersect at the  
7 "foot" of the waveform. This point is aligned with  
8 the same point on the flow waveform.

9  
10 Frequency domain analysis provides information about  
11 steady-state (resistance) and pulsatile function  
12 (characteristic impedance) of the ocular  
13 circulation. In Fig. 5, the steady state resistance  
14 is shown in area A and the characteristic impedance  
15 in area B. These signals are stored in digital form  
16 and the digitised signals are amenable to analysis  
17 in the time domain with the application of  
18 mathematical models to interpret waveshape changes  
19 in relation to the mechanical properties of the  
20 ocular circulatory bed.

21  
22 The present invention is highly advantageous with  
23 respect to the prior art because it provides a non-  
24 invasive method and apparatus for measuring vascular  
25 impedance and in particular, through interrogation  
26 of the wave shape, of the linear velocity profile of  
27 the blood bolus in the retrobulbar circulation.

28 Previously, invasive techniques had only been  
29 thought capable of providing information on the  
30 linear velocity profile. Such techniques are

31 expensive and cannot be used to obtain repeat  
32 results over a period of time for the same subject.



1 The present invention therefore allows a physician  
2 to monitor changes in the microcirculation of the  
3 eye and to extrapolate the data to make clinical  
4 judgements in various disease states associated with  
5 an increase in cardiovascular events.

6  
7 The present invention is applicable in a number of  
8 areas of clinical research. Some examples are given  
9 below.

10  
11 It has been recognised for many years that  
12 characteristic changes in the arterial pressure  
13 pulse contour occur in many disease states and with  
14 physiological and pharmacological interventions.  
15 Alteration in arterial waveform morphology typically  
16 involves a steepening of the diastolic decay and a  
17 diminution in the amplitude and duration of the  
18 oscillatory waveform that distorts the proximal part  
19 of diastole from a pure monoexponential. The  
20 oscillatory diastolic waveform arises from wave  
21 reflection and damped resonance occurring in the  
22 arterial tree with the major sites of reflected  
23 waves originating in smaller arteries and  
24 arterioles. Loss of the oscillatory diastolic  
25 waveform is recognised as an early marker of altered  
26 vessel wall properties that identifies impaired  
27 pulsatile function of arteries as it can be found in  
28 patients at increased cardiovascular risk without  
29 alteration in total peripheral resistance. This has  
30 been demonstrated in patients with diabetes mellitus  
31 and cigarette smokers. Whilst the microvascular  
32 changes associated with diabetes are well

1 recognised, the structural changes that are commonly  
2 found in the arterioles of smokers and rarely in  
3 non-smokers, are less well appreciated. These  
4 microvascular abnormalities may account for the  
5 common occurrence of microinfarcts found in  
6 association with diabetes and cigarette smoking that  
7 have hitherto gone unrecognised.

8

9 Analysis of the arterial pressure pulse waveform can  
10 also be useful in identifying the haemodynamic  
11 action of drug therapy not detected by the  
12 traditional measurement of peripheral resistance.

13

14 Improvements and modifications may be incorporated herein  
15 without deviating from the scope of the invention.

FIG. 1

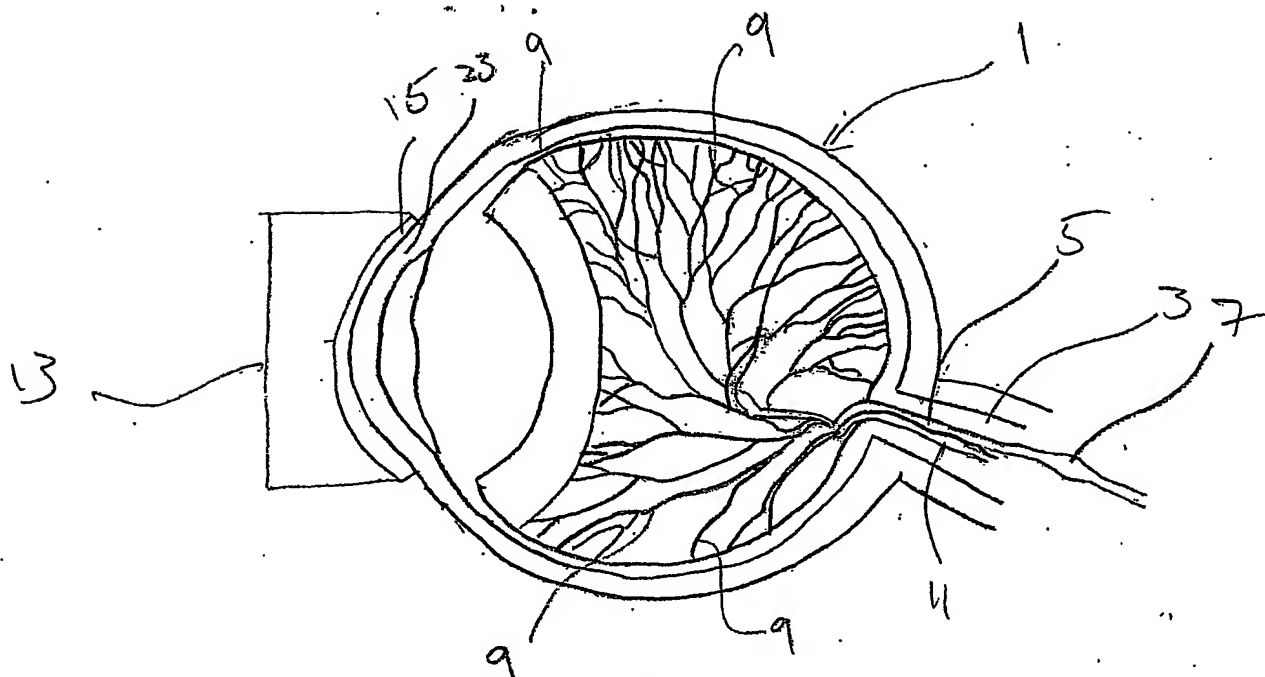
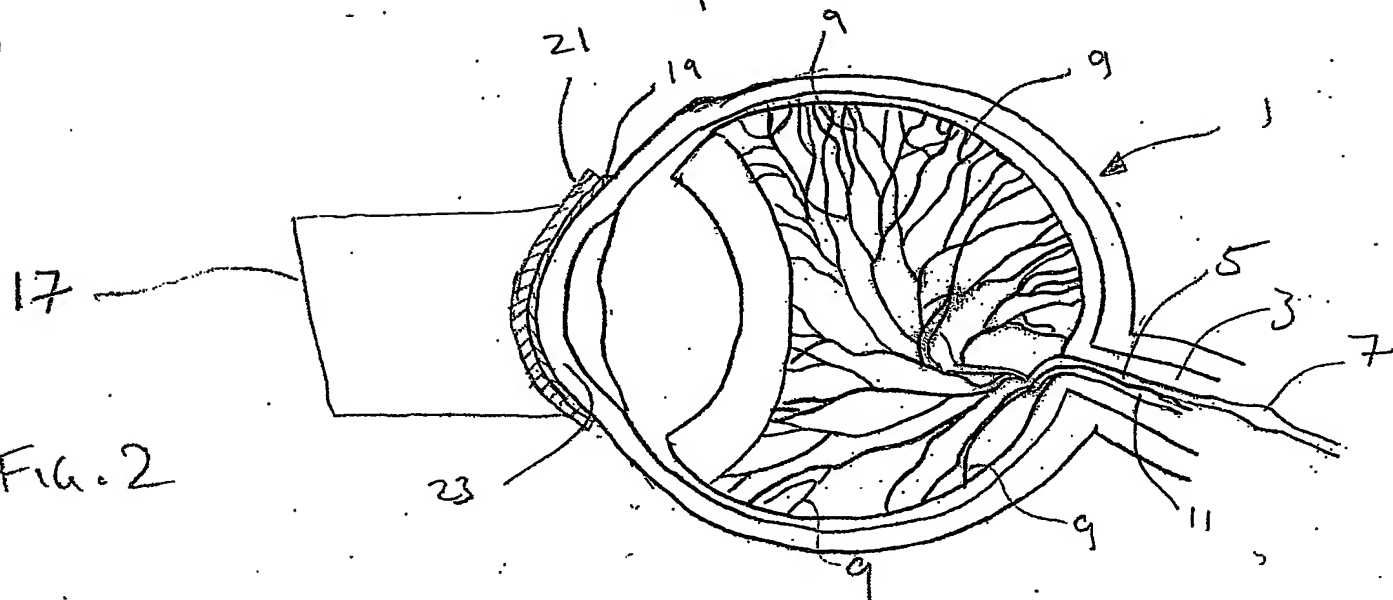


FIG. 2



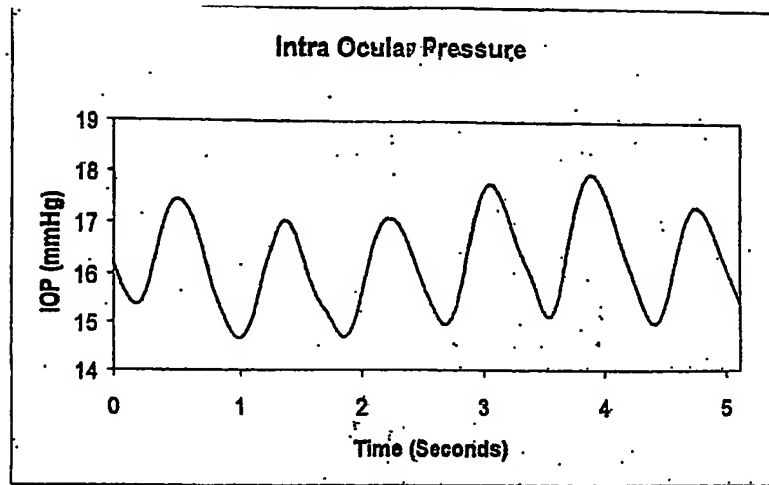


FIG-3

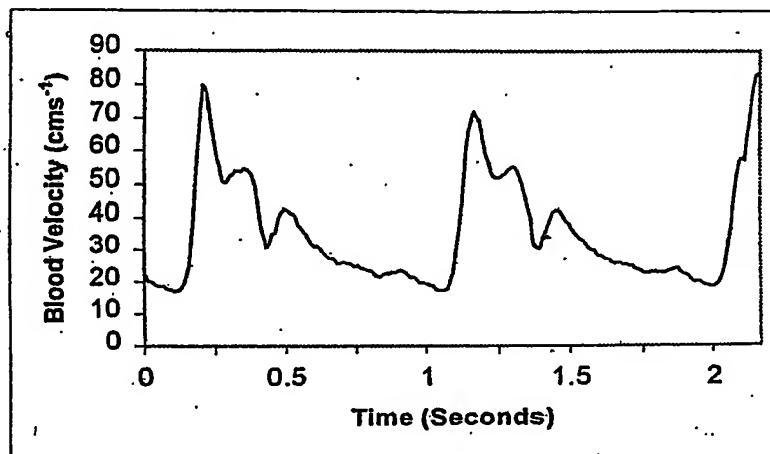


FIG. 4

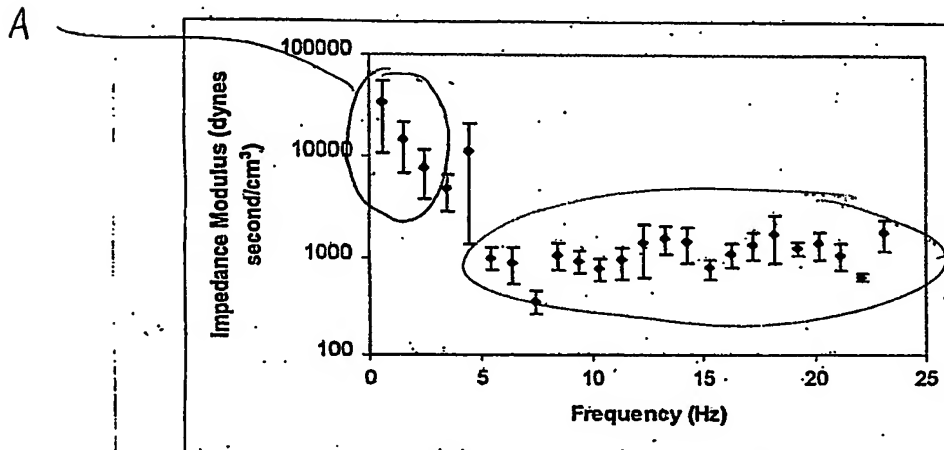


FIG-5

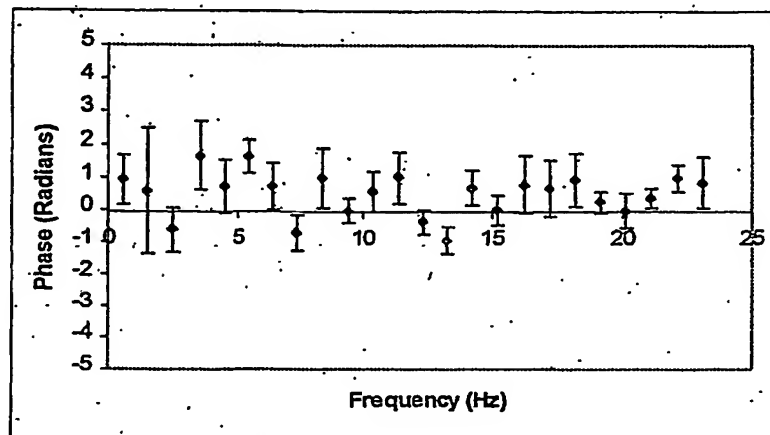


FIG. 6

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